Ref: Ro J Med Pract. 2024;19(4)
DOI: 10.37897/RJMP.2024.4.12

Computational profiling of antidepressants-induced molecular docking with placental proteins (IGFBP-1, PlGF-1 and GATA3)

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Abstract

Background. *Antidepressants readily penetrate the intrauterine environment, potentially influencing the genetic expression of specific genes in the fetal portion of the placenta. Nevertheless, there is a lack of understanding regarding the precise impact of these medications on placental proteins, which play critical roles in embryonic development.*

Methods. *Therefore, investigating their interaction with placental proteins is crucial. Utilizing computational analysis and molecular docking software, this study explores the interactions between ten antidepressant medications and the proteins IGFBP-1, PlGF-1, and GATA3 through dynamic simulation.*

Results. *The findings from molecular docking reveal a clear inclination of all drugs to bind with these proteins, albeit with varying degrees of affinity. Certain drugs (Trazodone, Amitriptyline, Nortriptyline, and Mirtazapine) exhibit high affinities for these proteins, while others show lower affinities (Desvenlafaxine, Phenelzine, and Tranylcypromine). The affinity values for IGFBP-1 and PlGF-1 ranged from -6.8 to -3.9 kcal/mol, with an average of -5.9 kcal/mol. In comparison, the affinity range for the GATA3 protein was -7.8 to -5.1 kcal/mol.*

Conclusion. *The molecular dynamics simulation of the four drugs with high affinity to proteins revealed that, except for Trazodone, they did not maintain stability within acceptable limits. Interestingly, Trazodone showed signs of stability with the IGFBP-1 protein throughout the molecular dynamics simulation. These findings may indicate that Trazodone potentially influences embryonic development, raising safety concerns for maternal-fetal health. Choosing the safest antidepressants requires balancing their mental health benefits with their potential molecular effects on placental proteins, ensuring the well-being of both mother and fetus during pregnancy. Further research and clinical guidelines should explore the interplay between antidepressant affinities and maternal-fetal health outcomes for a more informed approach to perinatal mental health care.*

Keywords: molecular docking, antidepressants, placental proteins, IGFBP-1, PlGF-1, GATA3

INTRODUCTION

Depression recognized as a pathological condition, stands as the most prevalent mental health disorder in women, particularly during pregnancy [1-3]. Peripartum mental disorders, such as anxiety and depression, are widespread, with maternal depression being linked to adverse outcomes. Antepartum anxiety and depres-

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Article History:
Received: 1 May 2024
Accepted: 17 December 2024

sion exhibit distinct and cumulative negative effects on both maternal and fetal outcomes [4-7]. Consequently, effective treatment for maternal depression may necessitate the use of antidepressant medications [3,8-9]. In light of the elevated prevalence of depression among pregnant women, exploring the intricate connection between this mental health condition and the indispensable use of antidepressant medications becomes imperative. This exploration is particularly crucial in unraveling the potential impacts of antidepressants on essential placental proteins. Antidepressant medications, particularly those falling under the selective serotonin reuptake inhibitors (SSRIs) class, are known to cross the human placenta [10] thereby impacting neonatal health [11].

Antidepressants can impact fetal growth and contribute to the development of congenital malformations by influencing the occurrence of genetic mutations and altering the characteristics of proteins [12-13]. Recently, increased attention has been directed toward exploring the potential connection between perinatal antidepressant consumption and adverse neonatal outcomes [4,14-17]. Recognizing the importance of pregnant women taking antidepressants to protect both themselves and their fetuses, the careful selection of the most appropriate medication is crucial.

In recent years, there has been a growing focus on investigating the potential link between perinatal antidepressant consumption and adverse neonatal outcomes. This study specifically delves into the effects of ten antidepressant medications on three human placental proteins: IGFBP-1, PlGF-1, and GATA3, through computational analysis. IGFBP-1 (Insulin-like Growth Factor Binding Protein-1) is integral to embryogenesis, orchestrating the activity of insulin-like growth factors (IGFs) such as IGF-I and IGF-II.

By binding to IGFs, IGFBP-1 modulates their availability and activity, impacting critical processes in embryonic development, including cell proliferation, differentiation, and survival [18]. PlGF-1 (Placental Growth Factor-1), a member of the Vascular Endothelial Growth Factor (VEGF) family, emerges as a key player in placental development and angiogenesis. Expressed in the placenta, PlGF-1 actively promotes angiogenesis, a vital process for both embryonic development and post-natal growth. Its interactions with VEGF receptors underscore its significance in regulating blood vessel growth during pregnancy [19-20]. GATA binding protein 3 (GATA3), part of the transcription factor family, assumes a pivotal role in embryogenesis, contributing diverse functions to the development of various tissues and organs. From critical involvement in inner ear development to essential roles in kidney development, immune system maturation, breast development, cardiac development, and neural tube development, GATA3 emerges as a multifaceted regulator. Expressed in the placenta, it influences trophoblast cell differentiation and function. GATA3's context-dependent role in gene regulation is fundamental for the proper differentiation and function of diverse cell types during embryogenesis [21-22]. overview of the functions and regulatory mechanisms of IGFBP-1, PlGF-1, and GATA3 in embryonic development encapsulates the roles these proteins play in fundamental biological processes. To delve into the molecular intricacies of this phenomenon, our study employs advanced computational analysis, focusing on the effects of ten antidepressant medications on three key human placental proteins: IGFBP-1, PlGF-1, and GATA3. This nuanced approach aims to uncover the underlying molecular mechanisms, paving the way for a comprehensive understanding of the potential impact on embryonic development.

MATERIAL AND METHODS

The chemical structures of the drug molecules examined in the study were obtained from the Zinc 15 database website (Figure 1 A). Before initiating the molecular docking process, the ligands were prepared using the Virtual Screening Tool Python Prescription program (Version: PyRx-0.8). Selected for its efficiency and user-friendly interface in molecular docking. The energy minimization parameters were set as follows: Force Field: uff, Optimization Algorithm: Conjugate Gradients, Total number of steps: 200, Number of steps for update: 1, Stop if energy differences are less than: 0.1. The human placenta proteins studied were acquired from the Protein Data Bank website using the following identifiers (IGFBP-1 ID: 1zt3, PlGF-1 ID: 1fzv, GATA3 ID: 4hc9) (Figure 1 B). These proteins were then cleaned and prepared for the molecular docking process using the Discovery Studio software. The target functional site for each protein was determined as follows: The C-terminal domain for IGFBP-1 [23], the PlGF-1zFlt-1D2 complex for PlGF-1 [24], and the C-terminal zinc finger for GATA3 [25]. Molecular docking was performed using PyRx-0.8, and the Discovery Studio software was utilized to illustrate the interactions and binding sites between the proteins and the drugs studied. Following molecular docking, molecular dynamics simulations of the candidate drugs were conducted using the Schrödinger program. Used for molecular dynamics simulations due to its advanced algorithms and precision in modeling biomolecular systems. These simulations spanned a duration of up to 100 nanoseconds for both proteins and drugs.

RESULTS

Molecular Docking

Furthermore, each of the three proteins engaged in numerous bonds with the antidepressant drugs, show-

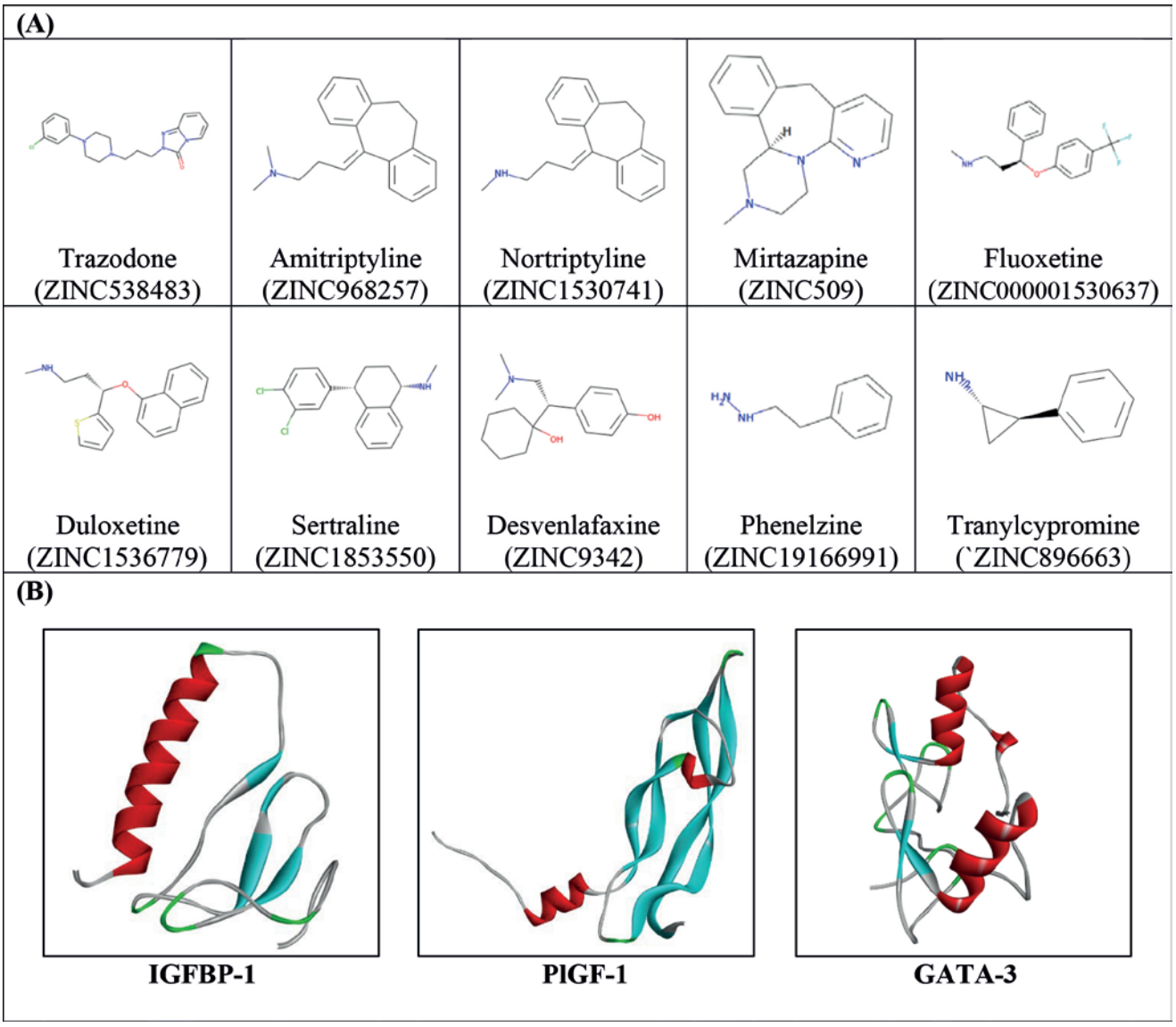

FIGURE 1. *(A) Depicts drug compositions obtained from the ZINC15 website, and (B) illustrates the structures of proteins obtained from the PDB Protein Data Bank website*

casing diversity in both type and number. Predominantly, these interactions manifested as traditional hydrogen bonds, non-traditional hydrogen bonds, and various other bond types such as van der Waals, Pi-Pi stacked, Alkyl, as detailed in Table 1-3 and illustrated in Figure 2. The average number of bonds formed by the proteins with drugs was (5), (4), and (6) for IGFBP-1, PlGF-1, and GATA3 proteins, respectively, as summarized in Table 1-3 and visualized in Figure 2. Observations revealed that Trazodone, Amitriptyline, Nortriptyline, and Mirtazapine exhibited the highest affinity kcal/mol. respectively for the IGFBP-1 protein (Table 1, Figure 2). Similarly, concerning the PlGF-1 and GATA-3 proteins, these drugs exhibited the highest affinity values, graded as follows: Trazodone, Nortriptyline, Mirtazapine, and Amitriptyline (Table 1-2, Figure 2). Furthermore, the findings indicated that Desvenlafaxine, Phenelzine, and Tranylcypromine exhibited the lowest affinity values kcal/mol. for both the IGFBP-1 and GATA-3 proteins. Similarly, with respect to the PlGF-1 protein, these drugs displayed the least affinity values in the following order: Desvenlafaxine, Tranylcypromine, and Phenelzine (Table 1-2, Figure 2). Having unveiled the intricate interactions and affinity patterns between antidepressant medications and the key placental proteins, the ensuing discussion delves into the nuanced implications of these findings, shedding light on their potential significance for maternal health and fetal development.

The findings from molecular docking investigations into the interactions between antidepressant drugs and human placental proteins revealed a clear inclination of all drugs to bind with the three specific proteins—IGFBP-1, PlGF-1, and GATA3—albeit with varying degrees of affinity. The affinity values for IGFBP-1 ranged between -6.8 to -4.5 kcal/mol with an average of -5.9 kcal/mol, as depicted in Table 1. Similarly, the affinity range for PlGF-1 was -6.0 to -3.9 kcal/mol with an average of

TABLE 1. *Affinity values and bonds established between drugs and the IGFBP-1 protein*

NO.	Drug	affinity (Kcal/mol)	Conventional H bond	others H bond	Number of residues implicated in interaction
1.	Trazodone	-6.8	GLU:179	LYS:237	7
2.	Amitriptyline	-6.8	TYR:202	GLU:179	5
3.	Nortriptyline	-6.8	-	GLU:218	5
4.	Mirtazapine	-6.3	-	GLY:236	4
5.	Fluoxetine	-6.0	ASN:235	GLY:236	7
6.	Duloxetine	-5.7	-	GLU:179	6
7.	Sertraline	-5.6	-	GLU:244	7
8.	Desvenlafaxine	-5.4	ARG:238	-	3
9.	Phenelzine	-5.1	TYR:202, GLY:236	-	4
10.	Tranylcypromine	-4.5	GLY:236	-	3
Average		-5.9			5.1

Affinity (Kcal/mol): Represents the strength of the binding between the drug and the protein. Lower values indicate stronger binding.
Conventional H bond: Refers to classic hydrogen bonds formed between the drug and specific residues in the protein.
Others H bond: Indicates non-conventional hydrogen bonds or weak interactions.
Number of residues implicated in interaction: Represents the total number of residues involved in the interaction between the drug and the protein.

TABLE 2. *Affinity values and bonds established between drugs and the PlGF-1 protein*

NO.	Drug	affinity (Kcal/mol)	Conventional H bond	others H bond	Number of residues implicated in interaction
1.	Trazodone	-6.0	CYS:70, GLY:71, GLU:73	GLY:71	6
2.	Nortriptyline	-5.7	GLY:31	CYS:35	7
3.	Mirtazapine	-5.5	-	TRP:30	3
4.	Amitriptyline	-5.5	-	CYS:111	4
5.	Sertraline	-5.5	CYS:35	-	3
6.	Fluoxetine	-5.0	CYS:113	GLY:31	8
7.	Duloxetine	-4.9	CYS:70	-	4
8.	Desvenlafaxine	-4.6	CYS:113	CYS:35	8
9.	Tranylcypromine	-4.3	-	CYS:69	2
10.	Phenelzine	-3.9	-	CYS:69	2
Average		-5.9			4.7

Affinity (Kcal/mol): Represents the strength of the binding between the drug and the protein. Lower values indicate stronger binding.
Conventional H bond: Refers to classic hydrogen bonds formed between the drug and specific residues in the protein.
Others H bond: Indicates non-conventional hydrogen bonds or weak interactions.
Number of residues implicated in interaction: Represents the total number of residues involved in the interaction between the drug and the protein.

-5.9 kcal/mol, as outlined in Table 2. Remarkably, the affinity range for GATA3 protein surpassed that of its counterparts, spanning between -7.8 to -5.1 kcal/mol with an average of -6.7 kcal/mol (Table 3).

Molecular Dynamics Simulation

Dynamic simulations were conducted for Trazodone, Amitriptyline, Nortriptyline, and Mirtazapine, which exhibited the highest affinity for IGFBP-1, PlGF-1, and GATA3 proteins. The findings revealed that these drugs did not attain stability with the proteins throughout the simulation period, as indicated by a Root Mean Square Deviation (RMSD) exceeding 5 Å. However, Trazodone demonstrated relatively greater stability with the IGFBP-1 protein, with its RMSD value remaining within acceptable limits (around 3 Å) (Figure 3).

DISCUSSION

The intricate relationship among maternal depression, antidepressant use during pregnancy, and their potential impact on placental proteins is central to our investigation. Let's explore the nuanced implications of our findings, connecting them to maternal health and

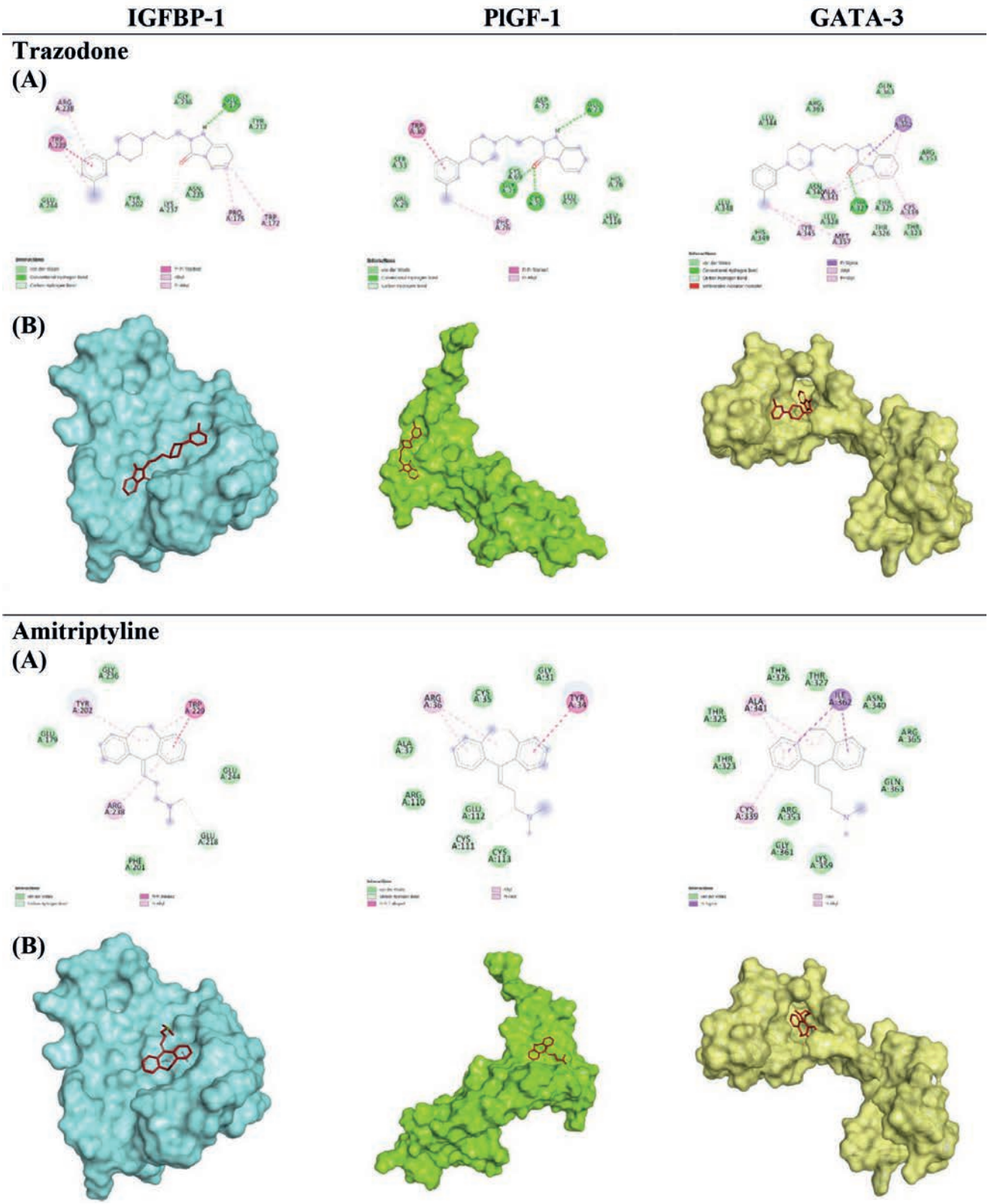

FIGURE 2. *(A) illustrates the 2D interactions, while Figure 2(B) depicts the binding mode between drugs and proteins*

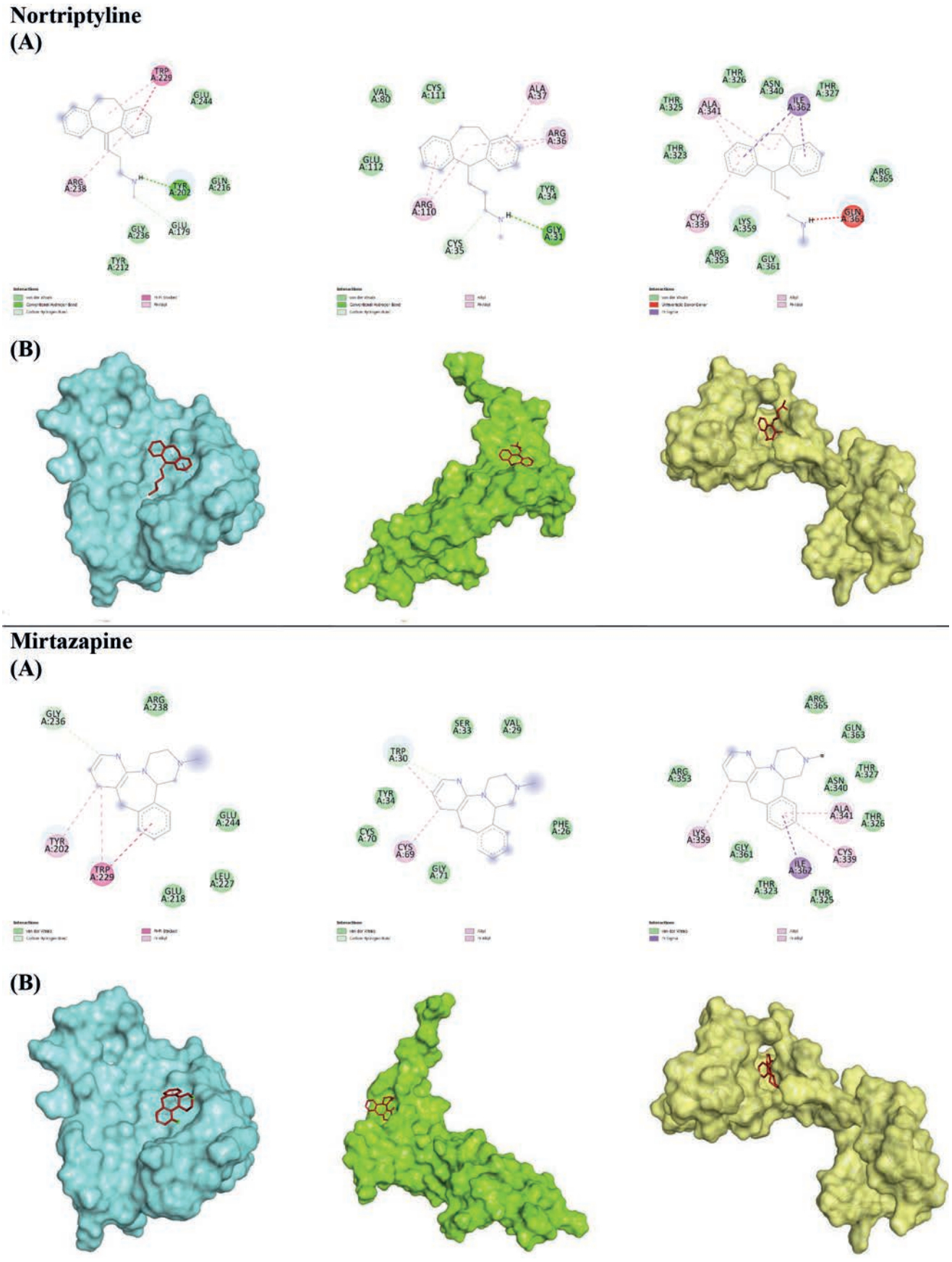
Nortriptyline
(A)
TRP A:229
GLU A:244
ARG A:238
TYR A:202
GLN A:216
GLY A:236
GLU A:179
TYR A:212
VAL A:80
CYS A:111
ALA A:37
ARG A:36
GLU A:112
TYR A:34
ARG A:110
GLY A:31
CYS A:35
THR A:326
ASN A:340
THR A:327
THR A:325
ALA A:341
ILE A:362
THR A:323
ARG A:365
CYS A:339
LYS A:359
GLN A:363
ARG A:353
GLY A:361
(B)
Mirtazapine
(A)
ARG A:238
GLY A:236
GLU A:244
TYR A:202
TRP A:229
LEU A:227
GLU A:218
SER A:33
VAL A:29
TRP A:30
TYR A:34
PHE A:26
CYS A:70
CYS A:69
GLY A:71
ARG A:365
GLN A:363
ARG A:353
THR A:327
ASN A:340
ALA A:341
THR A:326
LYS A:359
GLY A:361
CYS A:339
ILE A:362
THR A:323
THR A:325
(B)

FIGURE 2.

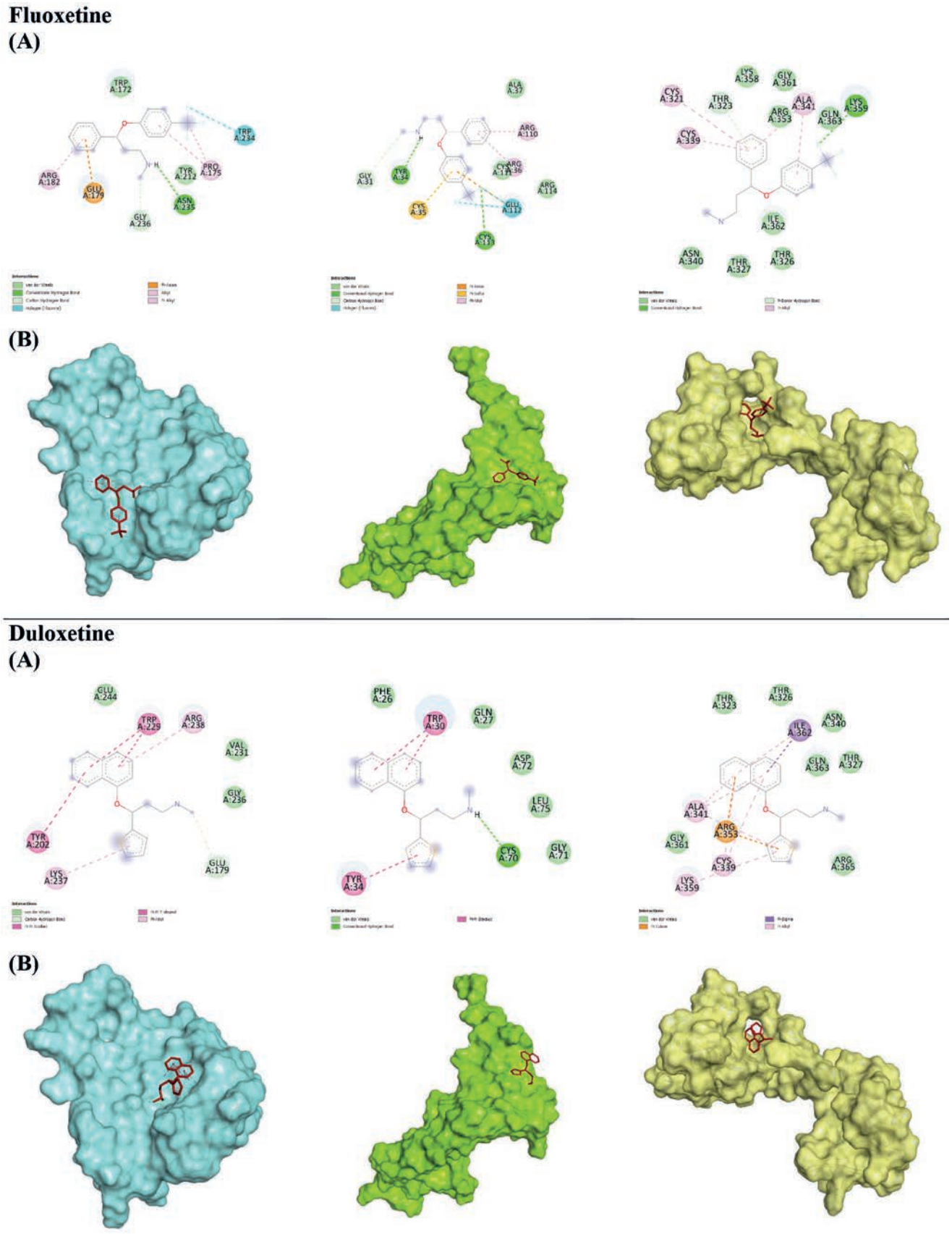
Fluoxetine
(A)
TRP A:172
TRP A:234
ARG A:182
GLU A:179
TYR A:212
PRO A:175
ASN A:235
GLY A:236
ALA A:37
ARG A:110
GLY A:31
TYR A:34
CYS A:35
GLU A:112
ARG A:114
CYS A:321
THR A:323
LYS A:358
GLY A:361
ALA A:341
LYS A:359
ARG A:353
GLN A:363
CYS A:339
ILE A:362
ASN A:340
THR A:327
THR A:326
(B)
Duloxetine
(A)
GLU A:244
TRP A:229
ARG A:238
VAL A:231
GLY A:236
TYR A:202
LYS A:237
GLU A:179
PHE A:26
TRP A:30
GLN A:27
ASP A:72
LEU A:75
CYS A:70
GLY A:71
TYR A:34
THR A:323
THR A:326
ILE A:362
ASN A:340
GLN A:363
THR A:327
ALA A:341
ARG A:353
GLY A:361
CYS A:339
ARG A:365
LYS A:359
(B)

FIGURE 2.

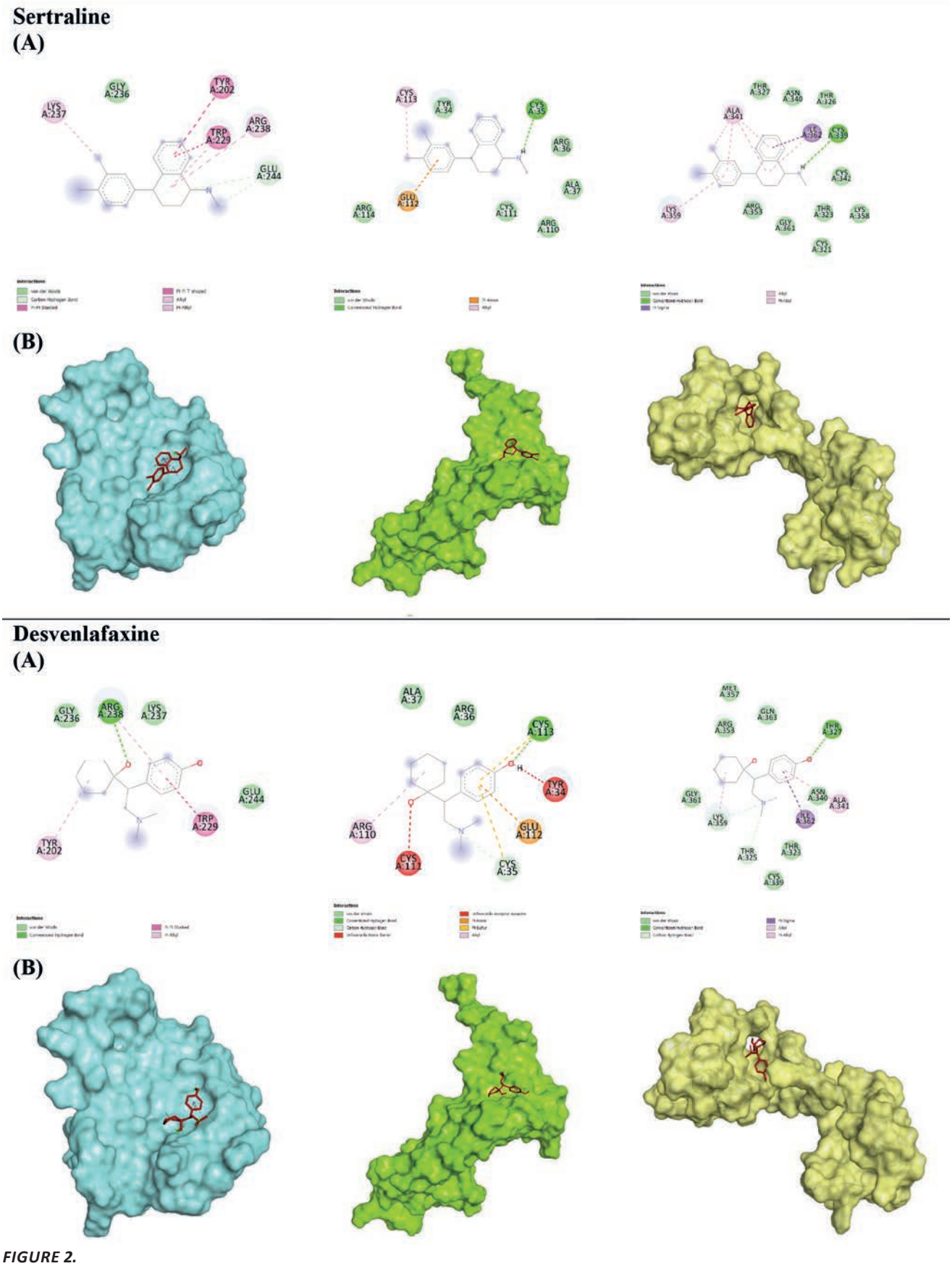
Sertraline
(A)
GLY A:236
TYR A:202
LYS A:237
ARG A:238
TRP A:229
GLU A:244
CYS A:113
TYR A:34
CYS A:35
ARG A:36
ALA A:37
GLU A:112
ARG A:114
CYS A:111
ARG A:110
THR A:327
ASN A:340
THR A:326
ALA A:341
CYS A:342
LYS A:339
ARG A:353
THR A:323
LYS A:358
GLY A:361
CYS A:321
(B)
Desvenlafaxine
(A)
GLY A:236
ARG A:238
LYS A:237
GLU A:244
TRP A:229
TYR A:202
ALA A:37
ARG A:36
CYS A:113
TYR A:34
ARG A:110
GLU A:112
CYS A:111
CYS A:35
MET A:357
GLN A:363
ARG A:353
THR A:327
GLY A:361
ASN A:340
ALA A:341
LYS A:359
THR A:325
THR A:323
CYS A:339
(B)

FIGURE 2.

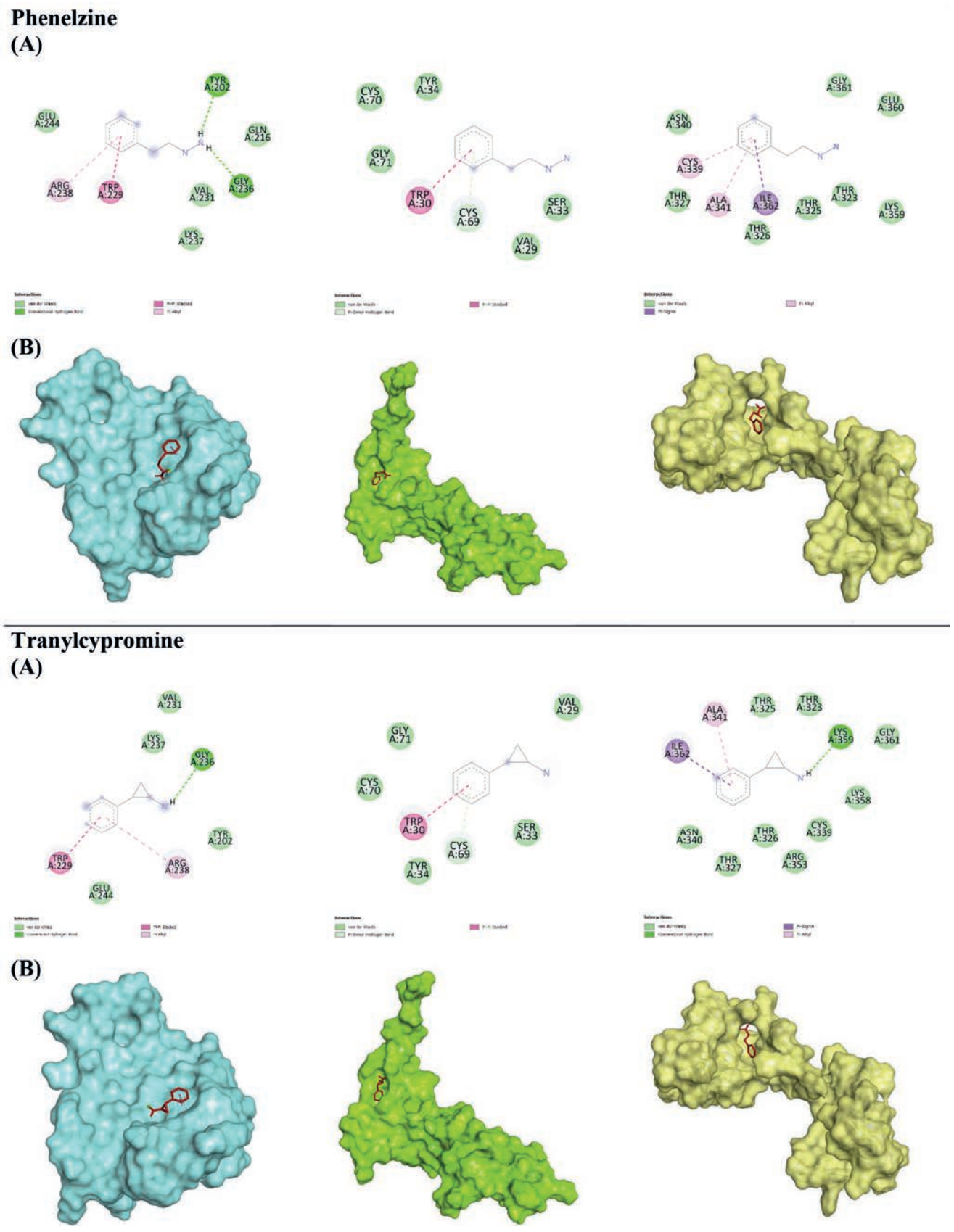
Phenelzine
(A)
TYR A:202
GLU A:244
GLN A:216
ARG A:238
TRP A:229
VAL A:231
GLY A:236
LYS A:237
CYS A:70
TYR A:34
GLY A:71
TRP A:30
CYS A:69
SER A:33
VAL A:29
GLY A:361
GLU A:360
ASN A:340
CYS A:339
THR A:327
ALA A:341
ILE A:362
THR A:325
THR A:323
LYS A:359
THR A:326
(B)
Tranylcypromine
(A)
VAL A:231
LYS A:237
GLY A:236
TYR A:202
TRP A:229
ARG A:238
GLU A:244
VAL A:29
GLY A:71
CYS A:70
TRP A:30
SER A:33
CYS A:69
TYR A:34
ALA A:341
THR A:325
THR A:323
ILE A:362
LYS A:359
GLY A:361
LYS A:358
ASN A:340
THR A:326
CYS A:339
THR A:327
ARG A:353
(B)

FIGURE 2.

ABLE 3. *Affinity values and bonds established between drugs and the GATA-3 protein*

NO.	Drug	affinity (Kcal/mol)	Conventional H bond	others H bond	Number of residues implicated in interaction
1.	Trazodone	-7.8	THR:327	THR:326	10
2.	Nortriptyline	-7.8	-	-	7
3.	Mirtazapine	-7.7	-	-	4
4.	Amitriptyline	-7.6	-	-	6
5.	Sertraline	-7.3	CYS:339	-	8
6.	Fluoxetine	-6.4	LYS:359	-	6
7.	Duloxetine	-6.2	-	-	9
8.	Desvenlafaxine	-5.9	THR:327	THR:325, LYS:359	6
9.	Phenelzine	-5.3	-	-	3
10.	Tranylcypromine	-5.1	LYS:359	-	3
Average		-6.7			6.2

Affinity (Kcal/mol): Represents the strength of the binding between the drug and the protein. Lower values indicate stronger binding.
Conventional H bond: Refers to classic hydrogen bonds formed between the drug and specific residues in the protein.
Others H bond: Indicates non-conventional hydrogen bonds or weak interactions.
Number of residues implicated in interaction: Represents the total number of residues involved in the interaction between the drug and the protein.

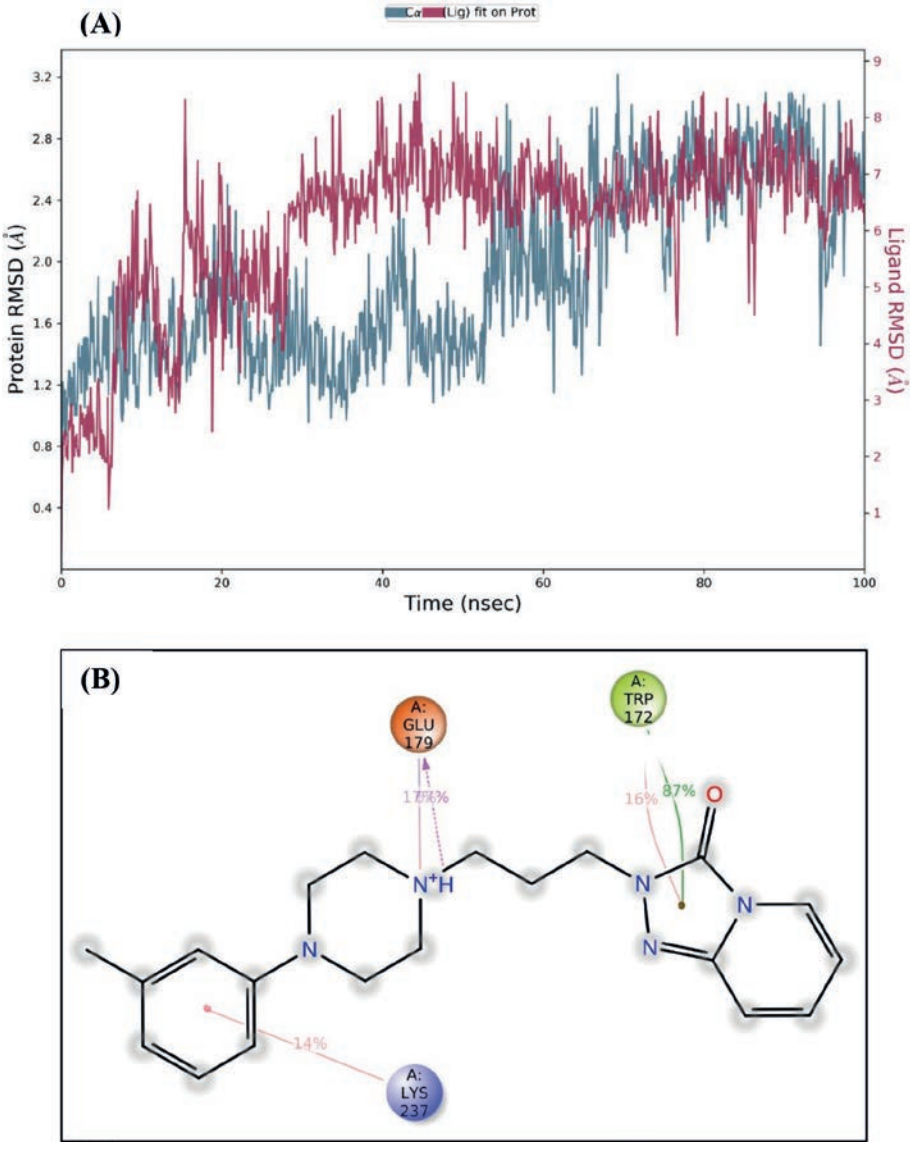

FIGURE 3. *(A) The Root Mean Square Deviation (RMSD) in angstroms (Å) of the IGFBP-1 protein with Trazodone was monitored throughout a 100 ns molecular dynamics (MD) trajectory. Both the ligand (Trazodone) and the receptor (IGFBP-1 protein) exhibited fluctuations within an acceptable range. Specifically, the IGFBP-1 protein, represented in green, displayed fluctuations within 2.5 Å, indicating stability towards the end of the simulation. Similarly, Trazodone, represented in maroon, showed relatively minor fluctuations in its binding to the protein and within its binding pocket, suggesting a stable confirmation throughout the simulation. (B) Results of 100 ns all-atom MD simulation of interactions docking poses with Trazodone*

fetal development. The prevalence of depression during pregnancy is well-established [1-3]. antepartum anxiety and depression exert distinct and cumulative negative effects on both maternal and fetal well-being, the use of antidepressant medications becomes a crucial aspect of maternal care [4-7].

Our study focuses on placental proteins IGFBP-1, PlGF-1, and GATA3 due to their integral roles in embryonic development [18-22]. The Docking analysis reveals a clear inclination of antidepressant drugs to bind with these proteins, indicating potential molecular interactions that could influence crucial processes in embryogenesis. Our finding exhibited varying degrees of affinity among antidepressant drugs and placental proteins. Understanding these affinity patterns is crucial for assessing the specificity of drug-protein interactions [26]. Trazodone, Amitriptyline, Nortriptyline, and Mirtazapine exhibit high affinities for IGFBP-1, PlGF-1, and GATA3 proteins.

Conversely, Desvenlafaxine, Phenelzine, and Tranylcypromine show low affinities. Due to the complexity of molecular systems, which typically comprise numerous particles, analytical determination of their properties is impractical. Molecular dynamics simulations offer a solution to this challenge through computational methods [27]. Therefore, molecular dynamics simulations were conducted for proteins exhibiting the highest binding affinity. Despite exhibiting high binding affinity with placental proteins, as indicated by the molecular docking results, the simulation findings suggest that these drugs do not establish stable interactions with placental proteins, except for Trazodone.

Recognizing the importance of pregnant women taking antidepressants to protect both themselves and their fetuses [3,8-9], our findings contribute to the ongoing discourse on the careful selection of appropriate medication. Clinicians should consider these molecular insights in their decision-making process, balancing the benefits of antidepressant use with potential impacts on placental proteins and, consequently, fetal development. Future research and clinical guidelines should explore the nuanced interplay between antidepressant affinities and maternal-fetal health outcomes for a more informed approach to perinatal mental health care [28]. The findings from this study suggest that the majority of the antidepressants examined did not significantly impact the functionality of the studied placental proteins, as they failed to establish a stable binding to the functional sites of these proteins throughout the simulation period.

However, Trazodone demonstrated stability within acceptable limits with the IGFBP-1 protein. This stability suggests a potential disruption in IGFBP-1's role in regulating fetal growth and development, warranting further investigation into its impact on fetal health. This observation raises concerns about Trazodone's potential negative effect on the protein and, consequently, its function during fetal development, which could contribute to the occurrence of congenital malformations [29]. Future studies should explore the long-term clinical implications of Trazodone use during pregnancy, investigate its effects on additional placental proteins, and validate these findings through in vivo and in vitro models.

CONCLUSION

In conclusion, this employing advanced computational analysis, sheds light on the complex interplay between antidepressant medications and crucial placental proteins. Choosing the safest medications, considering both mental health and the potential molecular influences of antidepressant use during pregnancy, is paramount. Future research should focus on assessing the safety profile of antidepressants with respect to placental functionality, integrating molecular and clinical approaches to ensure maternal and fetal health during pregnancy.

Conflict of interest: none declared
Financial support: none declared

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